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Predictive value of EEG findings at control of epileptic spasms for seizure relapse in patients with West syndrome

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ABSTRACT

Purpose: To evaluate the prognostic importance of electroencephalography (EEG) findings at cessation of epileptic spasms for seizure outcome.
Methods: We reviewed 71 children with West syndrome (cryptogenic 14) who had obtained control of epileptic spasms with initial treatment (adrenocorticotropic hormone (ACTH) 37, high-dose vitamin B_6 2, and antiepileptic drugs 32). According to the EEG findings at control of epileptic spasms, the subjects were divided into three groups: normal group (no epileptic activity, $n = 12$), abnormal group (residual epileptic activity without hypsarrhythmia, $n = 53$), and hypsarrhythmic group (persisting hypsarrhythmia, $n = 6$).
Results: Overall, 47 (66%) of the 71 patients (cryptogenic 4) had experienced relapses of seizures (epileptic spasms 23 and focal seizure 24) after initial control of epileptic spasms. Within symptomatic cases, seizure relapse rate varied widely from 0% (Down syndrome) to 100% (tuberous sclerosis), depending on underlying causes. Seizure relapse depended on the EEG findings at control of epileptic spasms. The normal group had a significantly lower seizure relapse rate (17%) in comparison with the abnormal group (75%), the hypsarrhythmic group (83%), and the epileptiform (abnormal plus hypsarrhythmic, 76%) group. No significant difference in seizure relapse rate was observed between non-hypsarrhythmic (normal plus abnormal, 65%) and hypsarrhythmic groups. At the last follow-up, normal group children also showed a favorable seizure prognosis (seizure control 100%).
Conclusions: A favorable seizure prognosis is associated with the disappearance of epileptic activity, but not the resolution of hypsarrhythmic pattern on EEG at control of epileptic spasms. We suggest that effective treatment for West syndrome should produce both cessation of epileptic spasms and disappearance of epileptic activity on EEG.
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1. Introduction

West syndrome is an age-related epileptic encephalopathy of infancy characterized by flexor/extensor type of epileptic spasms that usually occur in clusters, hypsarrhythmia on electroencephalography (EEG), and developmental arrest or regression. From evidence-based practice guidelines with a full literature review, it was concluded that adrenocorticotropic hormone (ACTH) and vigabatrin are the only drugs with proven efficacy for the first-line treatment of West syndrome.[1,2] However, long-term studies revealed that a substantial number of responders to either ACTH or vigabatrin had experienced relapse of epileptic spasms or development of other seizures.[1]

Previous studies have reported on both patient and treatment variables that seem to be implicated in the neurodevelopmental and seizure prognosis. Although these studies yielded conflicting results,[3–11] there is general agreement that outcomes are most dependent on underlying disorders and may be more favorable in cryptogenic etiology. Early recognition and prompt treatment may improve outcomes in some patients, particularly in those with cryptogenic West syndrome.[2,6] Other possible prognostic indicators associated with a favorable prognosis include normal development prior to the onset of epileptic spasms, normal imaging study results, absence of other seizure types, and sustained response to therapy without relapse.[12]

Most pediatric neurologists believe that effective treatment for West syndrome should produce both cessation of epileptic spasms and resolution of hypsarrhythmia on EEG. However, the prognostic

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importance of EEG findings at control of epileptic spasms has not been evaluated formally. To evaluate the predictive value of EEG findings at control of epileptic spasms for seizure outcome, we reviewed patients with newly diagnosed West syndrome who had cessation of epileptic spasms with initial treatment.

2. Materials and methods

We retrospectively reviewed the medical records of 164 patients (cryptogenic 28 and symptomatic 136) with newly diagnosed West syndrome who received initial treatment (defined as the first five therapeutic regimens) at Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan, between 1982 and 2008. In our institute, the drug selection was basically based on the treating physician's decision. The most commonly used drug as the initial treatment was high-dose vitamin B_6, followed by zonisamide, sodium valproate, and ACTH. Our ACTH treatment protocol was as follows. Before 2000, synthetic ACTH was given intramuscularly at 0.025 mg/kg per day for 2 weeks, then gradually tapered off to once every other day for 2 weeks, twice weekly for 2 weeks, and then once a week for 2 weeks (daily ACTH treatment). Thereafter, shortened ACTH treatment was introduced[13]; ACTH (0.025 mg/kg) was administered seven times on every other day for 2 weeks. Only patients with persistent epileptic spasms received additional therapy for 1 or 2 weeks with the same daily dose of ACTH, which was tapered off over a few weeks. If treatment with one drug failed to control epileptic spasms completely at the time of the last dose (ACTH), or at the maximal dose (vitamin B_6 or antiepileptic drug), it was replaced by another treatment. Response to therapy was defined as total cessation of clinically defined epileptic spasms by parental and/or nursing observation for over 28 days.

In the initial treatment, 48 infants (cryptogenic 2 and symptomatic 46) failed to respond to the first- to fifth-choice therapeutic regimens. The remaining 116 patients (cryptogenic 26 and symptomatic 90) had achieved control of epileptic spasms for over 28 days with initial treatment. Of these 116 responders, the subjects of this study included 71 patients (cryptogenic 14 and symptomatic 57) who were followed regularly for at least three years after the cessation of epileptic spasms with initial treatment (8 first-choice drug responders, 14 second-choice drug responders, 24 third-choice drug responders, 13 fourth-choice drug responders, and 12 fifth-choice drug responders).

In all patients, prolonged video EEGs, including full wake and sleep cycle, were recorded before the first-choice drug was allocated, and within two weeks after cessation of epileptic spasms. Routine EEGs were performed during the initial treatment. All were well-documented cases with typical clinical epileptic spasms, and EEG changes of hypsarrhythmia or modified hypsarrhythmia at the active stage of clinically defined epileptic spasms. Hypsarrhythmia was characterized by chaotic, non-rhythmic, asynchronous, disorganized, high-voltage spike and slow-wave activity.[12] Modified hypsarrhythmia was defined according to Hrachovy et al.[14] The EEGs were re-evaluated by one pediatric neurologist blinded to the clinical presentation. We compared his assessment with previous EEG reports. Differences were resolved using judgment by another pediatric neurologist. On the basis of the EEG findings at control of epileptic spasms, the subjects were divided into three groups: normal group (no epileptic activity with or without normal background EEG), abnormal group (residual epileptic activity without hypsarrhythmia), and hypsarrhythmic group (persisting hypsarrhythmia or modified hypsarrhythmia). We compared the clinical (age at onset, sex, classification, and etiology) and initial treatment parameters (treatment lag, effective drug, number of drugs used before cessation of epileptic spasms, and time to response from onset) among the three groups. Time to response from onset is defined as the time from onset of epileptic spasms to their cessation. Seizure outcome (seizure relapse and seizure control at last follow-up) and EEG findings at last follow-up were also compared. In this study, seizure relapse was defined as development of any type of seizure after initial control of epileptic spasms, including both relapse of epileptic spasms and progression to other epilepsy. Children were considered cryptogenic if they fulfilled the following criteria: (a) no known associated etiology, (b) normal development and neurologic examination before onset of epileptic spasms, (c) no previous seizure, and (d) normal brain imaging. The symptomatic cases were further classified into three etiologic subgroups depending on the timing of presumed causes: prenatal, perinatal, and postnatal subgroups.

Statistical studies were performed using Kruskal–Wallis test to compare clinical and initial treatment parameters among the three groups. Mann–Whitney *U* test and Fisher's exact probability test were used for comparisons between two groups. Chi-square test was used for comparison among the first- to fifth-choice drug responder groups. A difference was considered significant with a p value of 0.05 or less.

3. Results

The patients' clinical profiles are summarized in Table 1. There were 12 children in the normal group, 53 in the abnormal group, and six in the hypsarrhythmic group. We found no significant differences in gender distribution and age at onset among the three groups. In the normal group, seven infants were classified as cryptogenic and five as symptomatic. In contrast, both abnormal and hypsarrhythmic groups showed a predominance of symptomatic cases. There were also no significant differences in treatment lag and the number of drugs used before cessation of epileptic spasms among the three groups. The mean time to response from onset did not differ among the three groups, and the median values were similar among the groups (normal group, 2.0 months; abnormal group, 2.0 months; hypsarrhythmic group, 1.9 months). Thirty-seven patients (ACTH responders) had cessation of epileptic spasms after ACTH treatment (daily ACTH treatment 23, and shortened ACTH treatment 14). Of the remaining 34 infants (non-ACTH responders), including three who had failed to respond to ACTH (daily ACTH treatment 2, and shortened ACTH treatment 1), two infants had remission of epileptic spasms with high-dose vitamin B_6 therapy and 32 responded to antiepileptic drugs. ACTH responders accounted for half or more of the patients in the normal (6/12) and abnormal groups (30/53), while there was only one ACTH responder in the hypsarrhythmic group (1/6). Effective antiepileptic drugs were similar in the three groups.

Seizure outcomes are shown in Table 2. There were no significant differences in age at last follow-up among the three groups. Overall, 47 (66%) of the 71 patients had experienced relapses of seizures during the course of illness. Regarding types of recurrent seizure, none had generalized seizures. Epileptic spasms recurred in 23 patients, and focal seizures developed in 24 patients. We found no significant ($p = 0.44$) difference in seizure relapse rate among the five (first- to fifth-choice drug) responder groups (first-choice drug responders 6/8, second-choice drug responders 8/14, third-choice drug responders 17/24, fourth-choice drug responders 9/13, and fifth-choice drug responders 7/12). The mean time from initial control of epileptic spasms to seizure relapse was significantly shorter ($p = 0.0003$) in patients who showed relapse of epileptic spasms (mean, 7.0 months; range, 1.5–24 months) than in those who developed focal seizure (mean, 51.8 months; range, 1.5–173 months) (Fig. 1). Symptomatic patients showed a higher relapse rate (75%) than cryptogenic patients (29%) (Table 2). Etiology and seizure relapse rate in patients with symptomatic West syndrome are shown in Table 3. Both abnormal and

Table 1
Clinical profile.

Parameters	Total ($n=71$)	Normal group ($n=12$)	Abnormal group ($n=53$)	Hypsarrhythmic group ($n=6$)	p-Value
Sex (male/female)	45/26	8/4	33/20	4/2	0.94
Age at onset (mean ± SD, months)	6.9 ± 3.4	6.6 ± 2.6	6.9 ± 3.5	7.7 ± 4.2	0.90
Classification					
Cryptogenic	14	7*	6	1	0.001
Symptomatic	57	5*	47	5	
Prenatal	26	2	21	3	
Perinatal	25	3	21	1	
Postnatal	6	0	5	1	
Treatment lag (mean ± SD, weeks)	4.9 ± 5.3	4.9 ± 4.3	4.8 ± 5.6	6.0 ± 5.0	0.60
Time to response from onset (months)					
Mean ± SD	3.2 ± 3.9	3.3 ± 3.7	3.2 ± 4.0	2.8 ± 3.0	0.83
Median (range)	2.0 (0.3–21.3)	2.0 (0.75–14)	2.0 (0.3–21.3)	1.9 (1.0–9.0)	
No. of drugs used before cessation of epileptic spasms (mean ± SD)	3.1 ± 1.2	3.2 ± 1.1	3.2 ± 1.1	2.2 ± 1.6	0.18
Effective drug					
ACTH	37	6	30	1	0.23
B_6	2	0	1	1	
AEDs	32	6 (VPA 3, ZNS 2, NZP 1)	22 (VPA 8, ZNS 7, CZP 4, NZP 1, AZA 1, PHT 1)	4 (VPA 2, ZNS 2)	

ACTH = adrenocorticotropic hormone; B_6 = high-dose vitamin B_6; AEDs = antiepileptic drugs; VPA = sodium valproate; ZNS = zonisamide; NZP = nitrazepam; AZA = acetazolamide; CZP = clonazepam; PHT = phenytoin.
* Significantly different from abnormal group ($p < 0.05$).

Table 2
Seizure outcome.

Group	Total ($n=71$)	Normal group ($n=12$)	Abnormal group ($n=53$)	Hypsarrhythmic group ($n=6$)	p-Value
Age at last follow-up (years)					
Mean ± SD	12.0 ± 5.7	9.7 ± 5.6	12.6 ± 5.8	11.9 ± 4.8	0.29
(Range)	(3.5–27.7)	(3.7–20.8)	(3.5–27.7)	(4.7–17.3)	
Seizure relapse, no. (%)					
Overall	47 (66%)	2 (17%)*,**	40 (75%)	5 (83%)	0.0003
Cryptogenic	4 (29%)	1 (14%)	2 (33%)	1 (100%)	0.15
Symptomatic	43 (75%)	1 (20%)*	38 (81%)	4 (80%)	0.03
Seizure type at relapse, no.					
Epileptic spasms	23	1	21	1	
Focal seizure	24	1	19	4	–
Generalized seizure	0	0	0	0	
Seizure control at last follow-up, no. (%)	44 (62%)	12 (100%)*,**	29 (55%)	3 (50%)	0.008
EEG normalization at last follow-up, no. (%)	19 (27%)	11 (92%)*,**	9 (17%)	0 (0%)	<0.0001

* Significantly different from abnormal group ($p < 0.05$).
** Significantly different from hypsarrhythmic group ($p < 0.05$).

hypsarrhythmic groups included all three etiologic subgroups, while there was no postnatal subgroup in the normal group. Seizure relapse rate may vary depending on etiologic subgroups or underlying disorders. All six cases of postnatal origin (infantile intracranial hemorrhage and encephalopathy) had relapsed. Seizures recurred in all seven children with tuberous sclerosis, and in all four with brain anomaly. In contrast, none of four patients with Down syndrome had seizure relapses regardless of EEG findings.

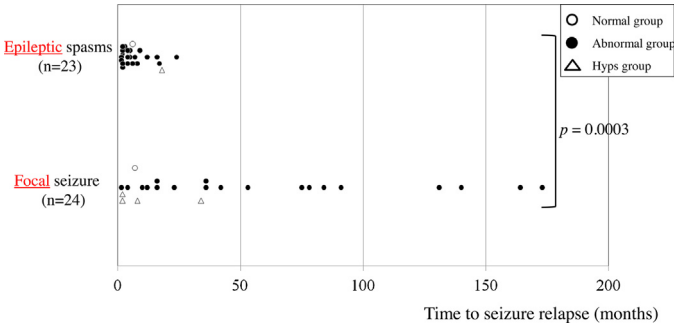

Fig. 1. Overall, 47 (66%) of the 71 patients had experienced relapses of seizures (epileptic spasms 23, focal seizure 24) after initial cessation of epileptic spasms. The mean time from initial control of epileptic spasms to seizure relapse was significantly shorter ($p = 0.0003$) in patients (upper) who showed relapse of epileptic spasms (mean, 7.0 months; range, 1.5–24 months) than in those (lower) who developed focal seizure (mean, 51.8 months; range, 1.5–173 months). Hyps = hypsarrhythmia.

A marked difference ($p = 0.0003$) was observed in seizure relapse rate among the groups (Table 2): only two (17%) of 12 normal-group children had seizure relapse, while 40 (75%) of 53 abnormal-group patients and five (83%) of six in the hypsarrhythmic group had relapsed after initial control of epileptic spasms. The differences reached statistical significance between normal and abnormal groups ($p = 0.0003$), and between normal and hypsarrhythmic groups ($p = 0.0062$). To focus on the disappearance of epileptic paroxysm, we then combined the data of the abnormal and hypsarrhythmic groups as an epileptiform group. The normal group (2/12) had a significantly ($p = 0.0002$) lower seizure relapse rate than the epileptiform group (45/59) (Fig. 2, left). In a separate analysis of cryptogenic and symptomatic cases, this low relapse rate of the normal group was confirmed in the symptomatic subgroup (normal group 1/5 vs. epileptiform group 42/52, $p = 0.01$). In the cryptogenic subgroup, the normal group (1/7) showed a lower seizure relapse rate than the epileptiform group (3/7), but the difference did not reach significance ($p = 0.17$).

Table 3
Etiology and seizure relapse rate in patients with symptomatic West syndrome.

Etiology	Total	Normal group	Abnormal group	Hypsarrhythmic group
Relapse rate (relapse cases/total cases)	75% (43/57)	20% (1/5)	81% (38/47)	80% (4/5)
Prenatal				
Down syndrome	0% (0/4)	0% (0/1)	0% (0/2)	0% (0/1)
Microcephalus	0% (0/1)	–	0% (0/1)	–
NF-1	100% (1/1)	–	100% (1/1)	–
Tuberous sclerosis	100% (7/7)	100% (1/1)	100% (5/5)	100% (1/1)
Brain anomaly	100% (4/4)	–	100% (4/4)	–
NKH	100% (1/1)	–	–	100% (1/1)
Congenital CMV infection	100% (1/1)	–	100% (1/1)	–
Unknown	86% (6/7)	–	86% (6/7)	–
Perinatal				
HIE	67% (8/12)	0% (0/1)	73% (8/11)	–
LBWI	33% (1/3)	0% (0/1)	50% (1/2)	–
ICH	67% (4/6)	0% (0/1)	75% (3/4)	100% (1/1)
PVL	100% (2/2)	–	100% (2/2)	–
Infarction	100% (2/2)	–	100% (2/2)	–
Postnatal				
Infantile ICH	100% (3/3)	–	100% (3/3)	–
Encephalopathy	100% (3/3)	–	100% (2/2)	100% (1/1)

NF-1 = neurofibromatosis type 1; NKH = non-ketotic hyperglycinemia; CMV = cytomegalovirus; HIE = hypoxic–ischemic encephalopathy; LBWI = low-birth-weight infant; ICH = intracranial hemorrhage; PVL = periventricular leukomalacia.

Although convincing evidence is lacking, most pediatric neurologists believe that effective treatment for West syndrome should produce both cessation of epileptic spasms and resolution of hypsarrhythmia on EEG. Therefore, we combined the data of normal and abnormal groups as a non-hypsarrhythmic group with a focus on the resolution of hypsarrhythmia. However, we found no significant difference ($p = 0.58$) in seizure relapse rate between non-hypsarrhythmic (42/65) and hypsarrhythmic groups (5/6) (Fig. 2, right).

At the last follow-up, there were significant differences in seizure control ($p = 0.008$) and EEG normalization ($p < 0.0001$) among the three groups (Table 2). All normal group patients (12/12) achieved seizure control, in contrast to the abnormal group (29/53) and the hypsarrhythmic group (3/6). EEG normalization was observed in 11 (92%) of 12 cases in the normal group, and in nine (17%) of 53 in the abnormal group. In contrast, none of the hypsarrhythmic group achieved EEG normalization. The differences of both parameters reached significance between normal and abnormal groups (seizure control: $p = 0.0027$, EEG normalization: $p < 0.0001$), and between normal and hypsarrhythmic groups (seizure control: $p = 0.02$, EEG normalization: $p = 0.0004$).

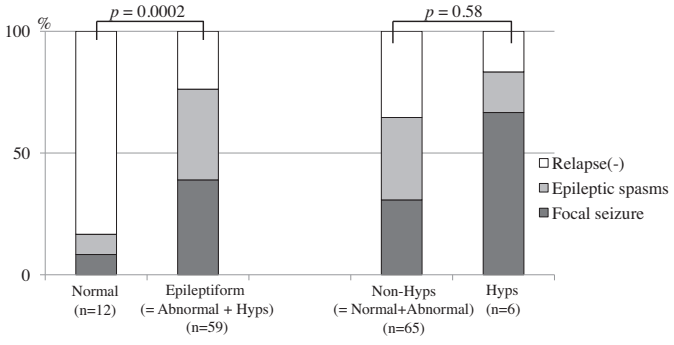

Fig. 2. In this study, 47 (66%) of 71 children with West syndrome who had obtained control of epileptic spasms (>28 days) with initial treatment had experienced relapses of seizures (epileptic spasms 23 and focal seizure 24). According to the EEG findings at control of epileptic spasms, the subjects were divided into three groups: normal group (no epileptic activity, $n = 12$), abnormal group (residual epileptic activity without hypsarrhythmia, $n = 53$), and hypsarrhythmic group (persisting hypsarrhythmia, $n = 6$). To focus on the disappearance of epileptic paroxysm, we combined the data of the abnormal and hypsarrhythmic groups as an epileptiform group. The normal group (2/12) had a significantly ($p = 0.0002$) lower seizure relapse rate than the epileptiform group (45/59) (left). When the data of normal and abnormal groups were combined as a non-hypsarrhythmic group with a focus on the resolution of hypsarrhythmia, however, no significant difference ($p = 0.58$) in seizure relapse rate was observed between non-hypsarrhythmic (42/65) and hypsarrhythmic groups (5/6) (right). Hyps= hypsarrhythmia.

4. Discussion

Since the introduction of ACTH in 1958,[15] vigabatrin represents the only antiepileptic drug with proven efficacy for first-line treatment of West syndrome.[1] In Japan, however, vigabatrin has not yet been approved for use. A Japanese survey performed in 2005 revealed that pediatric neurologists used high-dose vitamin B_6 most frequently as the first-choice drug, followed by sodium valproate, zonisamide, and ACTH.[16] However, current Japanese guidelines for the treatment of West syndrome recommend that ACTH should be introduced within one month after onset, especially in patients with non-symptomatic West syndrome.[17] In our institute, the drug selection was basically based on the treating physician's decision. The most commonly used first-choice drug was high-dose vitamin B_6 before 1994. After 1995, zonisamide, which has been marketed since 1989, was also used as the first-choice drug. In this study, we reviewed the effectiveness of the drugs administered to 164 patients with newly diagnosed West syndrome between 1982 and 2008. Seventy-one percent (116/164) of the patients responded to the first- to fifth-choice drugs used as the initial treatment. This result suggests that the therapeutic regimens available in Japan had limited effectiveness in the initial treatment of West syndrome.

The West Delphi Group proposed two appropriate primary outcomes in the treatment of West syndrome: primary clinical outcome (defined as complete cessation of epileptic spasms) and primary electroclinical outcome (defined as complete cessation of epileptic spasms with resolution of hypsarrhythmia on EEG).[18] In retrospective ACTH short-term studies, the response rates for cessation of epileptic spasms (primary clinical outcome) ranged from 59% to 100%, and resolution of hypsarrhythmia from 57% to 97%.[1] However, little is known about how often the clinical response is associated with resolution of hypsarrhythmia.[18] In this study, 65 (92%) of the 71 subjects showed resolution of hypsarrhythmia, indicating that 92% of primary clinical responders were regarded as primary electroclinical responders in our study population. Of note, the majority of patients without resolution of hypsarrhythmia were non-ACTH (high-dose vitamin B_6, zonisamide, and sodium valproate)

responders. These non-ACTH therapeutic agents may have a weak effect on the EEG, in comparison with ACTH.

Most previous studies revealed that approximately 20–50% of patients who responded to ACTH had experienced relapse of seizures, but some researchers have documented rates as high as 62%.[1] The reported relapse rate after vigabatrin treatment ranged from 0% to 63%, depending on the study design and the follow-up period.[1,8,19,20] There are insufficient data on the relapse rates after treatment with other therapeutic regimens. In this study, 47 (66%) of 71 initial treatment responders had experienced seizure relapses (epileptic spasms in 23 children and focal seizures in 24). Symptomatic patients showed a higher relapse rate (75%) than cryptogenic patients (29%). Although the small number of patients is a limitation of this study, seizure relapse rate may vary widely depending on underlying causes within symptomatic cases: the relapse rate is high in some etiologies such as tuberous sclerosis (100%), in contrast to a low relapse rate in children with Down syndrome (0%). Further studies with more symptomatic patients are needed to confirm our results.

This is the first study in which the prognostic importance of EEG findings at control of epileptic spasms was evaluated in patients with West syndrome. Seizure relapse after initial treatment depended on EEG findings at control of epileptic spasms. Patients with no epileptic activity (normal group) had a significantly lower seizure relapse rate (17%), in comparison with children with residual epileptic activity without hypsarrhythmia (abnormal group, 75%), and those with persisting hypsarrhythmia (hypsarrhythmic group, 83%). We then combined the data with a focus on the disappearance of epileptic paroxysm or hypsarrhythmia. A significant difference in seizure relapse rate was observed between normal and epileptiform (abnormal plus hypsarrhythmic, 76%) groups, but not between non-hypsarrhythmic (normal plus abnormal, 65%) and hypsarrhythmic groups. In a further separate analysis of cryptogenic and symptomatic cases, we found a lower seizure relapse rate tendency in the normal group than in the epileptiform group, in each subgroup. These results showed that mere resolution of hypsarrhythmia at control of spasms did not decrease the risk of seizure relapse. Disappearance of epileptic activity may be associated with a sustained response without relapse after initial treatment. Furthermore, normal-group children had a favorable prognosis (seizure control 100% and EEG normalization 92%) at the last follow-up relative to the other two groups.

In conclusion, our study revealed that a favorable seizure prognosis is associated with the disappearance of epileptic activity on EEG at control of epileptic spasms. In addition to the cessation of epileptic spasms, effective treatment for West syndrome should be targeted to produce abolition of epileptic activity and resolution of hypsarrhythmic pattern. With currently available agents, however, we cannot expect epileptic activity to disappear even if the hypsarrhythmic pattern has resolved. New treatment options may be needed for improvement of seizure prognosis in patients with West syndrome. These options include development of a novel antiepileptic drug with a stronger effect on the EEG or individualized ACTH treatment protocol, in which the duration of ACTH treatment is extended or the dose of ACTH is increased, depending on EEG findings, for patients who respond clinically to ACTH treatment, but show no abolition of epileptic activity on EEG.

Conflict of interest statement

No conflicts of interest have been declared.

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